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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XXIX.[1] BIAROMATICS IN THE THIOPHENE SERIES. II. THE SYNTHESIS OF BIPHENYL TYPE COMPOUNDS CONTAINING THE THIOPHENE RING.[2]

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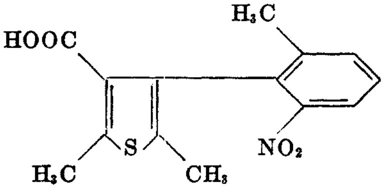
The successful resolution of 2,2′-dinitrodiphenic acid into optically active forms (1) opened an entirely new field of stereochemistry. Since that time, the phenomenon of restricted rotation has been amply demonstrated in the biphenyl series, but little work has been reported in the heterocyclics due to the difficulty of synthesis. In 1951 such investigations were extended into the thiophene series (2), and later in the same year the successful synthesis and resolution of an α-phenylthiophene was reported (3). This marked the first demonstration of restricted rotation in the field of mixed biaromatics.

The present work deals with the study of three β-phenylthiophenes, three 2,2′-bithienyls, and two 3,3′-bithienyls. It should be noted that this is the first instance of the synthesis of an unsymmetrically substituted mixed biaromatic containing four *ortho* substituted groups in which the benzene moiety is attached to the β-position of the thiophene ring. Furthermore, the preparation of symmetrically substituted bithienyls has been reported only in scattered instances in the literature (4). Hence, the study of the biphenyl type stereochemistry in a heretofore unavailable field is now rendered possible.

Before undertaking the synthesis of the β-phenylthiophene, it was necessary to consider the ease with which the thiophene moiety could be prepared and made to condense with a suitably substituted aromatic halide possessing approximately the same degree of reactivity. Also, certain steric relationships must be considered in order that the proposed structure exists in a non-coplanar form and so be capable of resolution into enantiomorphic forms. All these requirements are met by 2,5-dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid.



Accordingly, methyl 4-iodo-2,5-dimethyl-3-thenoate and 3-nitro-2-iodotoluene were selected as the starting materials for the proposed crossed Ull-

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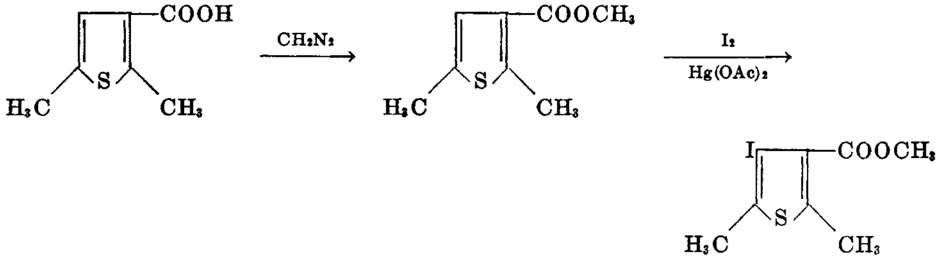
[1] For communication No. XXVIII of this series see Nord, Vaitiekunas, and Owen, *Fortschr. Chem. Forschg.*, **3**, 309 (1955).

[2] For preliminary communications see Jean, Owen, and Nord, *Nature*, **169**, 585 (1952) and Nord and Jean, *Naturwissenschaften*, **39**, 480 (1952).

mann reaction. The resulting ester and by-products were hydrolyzed, whereupon the desired acid was obtained in 30% yield. The methyl ester and amide served for further identification.

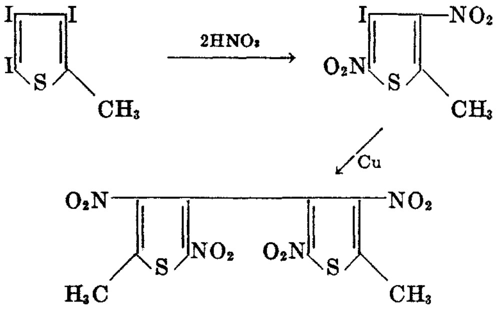
2,2′,5,5′-Tetramethyl-3,3′-bithienyl-4,4′-dicarboxylic acid was prepared by condensing two molecules of 4-iodo-2,5-dimethyl-3-thenoate in the presence of copper. The resulting diester was obtained in 35% yield, representing a substantial increase over that obtained from the corresponding bromo ester (5). Hydrolysis afforded the desired dibasic acid.

The thiophene moiety was prepared by the following series of reactions:



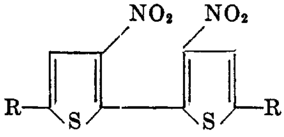
Since large quantities of 2,5-dimethylthiophene were required as the initial starting material, it was decided to improve the yields by a modification of the existing procedures. It was found that by reacting 2.5 moles of acetonylacetone with one mole of P_2S_5 and with the aid of mechanical stirring a yield of 87% could be obtained; this exceeds the previous high of 70% (6, 7).

During these investigations it was found desirable to prepare a 3,3′-bithienyl possessing four nitro groups in the *ortho* positions. This was achieved by condensing 4-iodo-3,5-dinitro-2-methylthiophene with copper in the usual manner. The thienyl halide was prepared by the method of Priestly and Hurd (8), wherein two of the iodine atoms of 3,4,5-triiodo-2-methylthiophene are replaced by nitro groups, as was attested to by the blue color test with 10% NaOH (9). These reactions are as follows:



It was found that the starting material in this series could be best prepared by modifying the procedure of Steinkopf and Hanske (10). This entailed the direct addition of iodine to a mixture of mercuric acetate and 2-methylthiophene in acetic acid at 95–100° to give an 82% yield of the product.

The 2,2′-bithienyls studied all possess nitro groups in the *ortho* positions and differ only with regard to the substituent in the *para* position as can be seen:



where R = NO_2, $COCH_3$, or $COOCH_3$

These compounds were prepared by condensing the corresponding 2-chlorothiophenes (11). It was found that the yields could be substantially increased and the purity of the product improved, if acetone was employed as the solvent for the extraction of the reaction mixture, and if acetic acid was selected as the solvent for recrystallization. In the latter instance, any copper salts that might be present and any amine byproduct that might have formed would be removed.

EXPERIMENTAL

The melting points as reported are uncorrected and were obtained with a Fisher-John Apparatus.

Materials. The *thiophene* used in these studies was obtained through the courtesy of the Monsanto Chemical Co., St. Louis, Mo. *2-Chlorothiophene* was purchased from the Eastman Kodak Company, Rochester, N. Y. The *silicone oil* was supplied through the courtesy of the General Electric Company, New York, N. Y. Baker's precipitated *copper* (J. T. Baker Chemical Company, Phillipsburg, N. J.) was the condensing agent employed throughout these studies.

2,5-Dimethylthiophene. In a 3-liter, three-necked flask, fitted with two reflux condensers (one in each side neck), and an oil-sealed mechanical stirrer in the center neck, were placed 285 g. (2.5 moles) of acetonylacetone and 220 g. (1.0 mole) of phosphorus pentasulfide (both of Tech. grade). With vigorous agitation, the mixture was heated by means of a free flame, first at one point and then at another, until evolution of gas caused the mixture to foam. Vigorous agitation broke up the foam, and the heat of the exothermic reaction was controlled by cooling with water. After the initial intensive reaction had subsided, the mixture was heated in an oil-bath for 1.5 hours. The liquid then was decanted into a 1-liter round-bottomed flask to which a suitable fractionating column was attached. The material then was distilled and the fraction boiling at 134–135° was collected. Redistillation over sodium gave a yield of 194 g. (87%) of 2,5-dimethylthiophene, b.p. 136–136.5°.

2,5-Dimethyl-3-acetothienone was prepared from 2,5-dimethylthiophene according to the procedure of Hartough and Conley (12), wherein acetylation was accomplished *via* an equimolar amount of acetic anhydride and the utilization of 85% orthophosphoric acid as the catalyst.

2,5-Dimethyl-3-thenoic acid was prepared from the above ketone *via* the hypochlorite oxidation procedure reported by these same authors (13).

Methyl 2,5-dimethyl-3-thenoate. 2,5-Dimethyl-3-thenoic acid (7.8 g., 0.05 mole) dissolved in ether was subjected to the action of excess diazomethane obtained *via* N-nitrosomethylurea. After removing the excess reagent, the solution was washed with 10% sodium bicarbonate and dried over potassium carbonate. Upon filtration and evaporation of the ether, there was obtained a residual liquid which on distillation *in vacuo* afforded 7.4 g. (87%) of a clear, colorless liquid, b.p. 97°/4 mm.; n_D^{27} 1.5238.

Anal. Calc'd for $C_8H_{10}O_2S$: C, 56.47; H, 5.88.

Found: C, 56.48; H, 5.81.

Methyl 4-iodo-2,5-dimethyl-3-thenoate. In a 500-ml. round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and thermometer, were placed 17 g. (0.10 mole) of methyl 2,5-dimethyl-3-thenoate and 32 g. of mercuric acetate in 300 ml. of glacial acetic acid. The solution was heated to 95°, and 26 g. of iodine was added with constant stirring, each portion being added only after the reaction mixture had become decolorized. After the final addition, the temperature was raised to 100° and the reaction mixture was stirred at that point for one hour. After cooling and adding 360 ml. of water, a yellow oil together with a crimson precipitate of mercuric iodide was obtained. The latter was filtered, and the filtrate containing the oil was extracted with ether. The ether layer was washed with 10% KI solution, until all the mercuric iodide was removed, and then was dried over potassium carbonate. The solution then was filtered, the ether removed on the steam-bath and the residual liquid distilled *in vacuo.* A clear, colorless liquid was obtained, b.p. 155–156°/8.5 mm., which solidified on freezing. The solid mass so obtained was allowed to crystallize from an alcohol-water mixture containing activated carbon (Norit) to yield 17.8 g. (60%) of colorless, white needles, m.p. 33.5–34.5°.

Anal. Calc'd for $C_8H_9IO_2S$: C, 32.43; H, 3.04.
Found: C, 32.33; H, 2.98.

2,2′,5,5′-Tetramethyl-4,4′-dicarbomethoxy-3,3′-bithienyl. Methyl 4-iodo-2,5-dimethyl-3-thenoate (2.96 g., 0.01 mole) was placed in a 6″ Pyrex test tube, which was immersed in a silicone oil-bath, the level of the ester being level with that of the oil-bath. Thermometers were placed in both the reaction tube and the bath. The mono ester then was heated to 230° and treated with 2.86 g. (0.045 mole) of Baker's precipitated copper in the course of 25 minutes, the temperature being maintained at 230–235° and constant agitation being provided by means of hand stirring with the thermometer. After the final addition, the reaction mixture was heated to 260° for 15 minutes. Extraction of the cooled reaction mass with ether and subsequent evaporation of the solvent afforded a red-brown oil, which was dissolved in ethanol in the presence of activated carbon (Norit) and allowed to crystallize. There were obtained 0.590 g. (35%) of light yellow plates, m.p. 50.5–51.5°. There was no melting point depression on admixture with an authentic sample (5) obtained from the corresponding mono bromo ester in 7.4% yield.

3-Nitro-2-iodotoluene was prepared by a modification of the procedure of Wheeler and Liddle (14), whereby a cold solution of sodium nitrite was added to a solution of 3-nitro-*o*-toluidine in dilute sulfuric acid at 0–5° with constant stirring. This increased the yield to 72%. 3-Nitro-*o*-toluidine was prepared according to the method of Meisenheimer and Hesse (15).

2,5-Dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid. Methyl 4-iodo-2,5-dimethyl-3-thenoate (5.33 g., 0.018 mole) and 3-nitro-2-iodotoluene (3.95 g., 0.015 mole) were placed in an 8″ test tube and thoroughly mixed. The tube was heated in an oil-bath, until the internal temperature rose to 225°. Then 7.62 g. (0.120 mole) of copper was added during the course of 50 minutes, while the internal temperature was maintained at 225–235°. After the final addition, the temperature was allowed to rise to 250° and was held at that point for 15 minutes. Upon cooling, the reaction mixture was thoroughly extracted with ether. The oily residue obtained upon evaporation of the solvent was saponified by refluxing with 20 ml. of 10% KOH for 4 hours. The mixture then was filtered to remove the alkali-insoluble black tar which had remained. The filtrate then was slowly acidified with dilute HCl to afford an orange-brown solid. This crude product was extracted with 80 ml. of hot benzene. Purification of the red-brown solution with activated carbon (Norit) for 20 minutes yielded an orange-red filtrate, which was concentrated to one-half of its volume and extracted with 10% NaOH. Acidification of the alkaline solution with dilute HCl precipitated an orange-yellow solid, which after recrystallization from an alcohol-water solution yielded 1.3 g. (30%) of yellow crystals, m.p. 211–212° with softening at 204–205°.

Anal. Calc'd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.46; Neut. equiv., 291.3.
Found: C, 57.32; H, 4.03; Neut. equiv., 288.9.

Methyl 2,5-dimethyl-4-(6'-methyl-2'-nitrophenyl)-3-thenoate. The corresponding acid (0.250 g., 0.00086 mole) was dissolved in ether and excess diazomethane was generated into the solution. Removal of excess reagent and the solvent afforded a yellow oil which was recrystallized from a hot alcohol-water mixture containing activated carbon (Norit). The yellow plates obtained (0.120 g., 46%) melted at 58–59°.

Anal. Calc'd for $C_{15}H_{15}NO_4S$: C, 59.01; H, 4.95.

Found: C, 58.65; H, 4.72.

2,5-Dimethyl-4-(6'-methyl-2'-nitrophenyl)-3-thenamide. To 50 ml. of chloroform and 1.3 ml. of thionyl chloride in a 200-ml. round-bottomed flask was added 0.250 g. (0.00086 mole) of the corresponding acid. The mixture was refluxed for 3 hours. After cooling, it was poured into a solution of 0.750 g. of NaOH in 18 ml. of ammonium hydroxide. The chloroform layer was separated and evaporated to dryness. The residual solid was dissolved in alcohol, treated with activated carbon (Norit), and brought to the cloud point with water. There was obtained 0.210 g. (80%) of fine yellow plates which softened at 162° and melted at 177–178°.

Anal. Calc'd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86.

Found: C, 58.02; H, 4.70.

3,4,5-Triiodo-2-methylthiophene. It was found that this substance could best be prepared by modifying the procedure of Steinkopf and Hanske (10). In a 2-liter round-bottomed flask, fitted with an oil-sealed mechanical stirrer, reflux condenser and thermometer, were placed 500 ml. of glacial acetic acid, 10 g. (0.102 mole) of 2-methylthiophene, and 96 g. (0.300 mole) of mercuric acetate. Stirring was initiated, and the solution was heated electrically until a temperature of 95° was attained. Then 78 g. (0.307 mole) of iodine was added in small portions, each portion being added only after the mixture had become decolorized. After the final addition, the temperature was raised to 100° and held at that point for one-half hour. After cooling, the mixture was diluted with 750 ml. of water, stirred for 20 minutes and allowed to stand overnight. The precipitate, which had formed, was washed with water until free of acid. Then it was stirred for 2 hours with 100 g. of KI in 1 liter of water in order to dissolve the mercuric iodide. Then it was filtered, washed with water, and recrystallized from an alcohol-water mixture containing activated carbon (Norit). There was obtained 38.9 g. (82%) of 3,4,5-triiodo-2-methylthiophene which melted at 98–100°.

4-Iodo-3,5-dinitro-2-methylthiophene. To an ice cold solution of 33 ml. of fuming nitric acid (*d.* 1.5), 9.2 g. (0.019 mole) of 3,4,5-triiodo-2-methylthiophene was added in small portions with constant stirring. The solution took on a red color due to the liberation of iodine. The reaction mixture then was poured into 180 g. of ice-water and the free iodine was removed with a saturated solution of sodium bisulfite. The yellow material, which had precipitated, was collected, washed with water until free of acid, and then washed with sodium bisulfite solution. After washing with water and alcohol, it was air-dried; the yield was 4.68 g. Upon recrystallization from an alcohol-water solution, a yellow solid (2.6 g., 43%) was obtained which melted at 122–124°.

Then 3.1 g. of this intermediate was dissolved in an ice-cold mixture of 19 ml. of concentrated nitric acid and 28 ml. of concentrated sulfuric acid and stirred for 30 minutes. The reaction mixture then was poured into ice-water and the precipitated product was treated with sodium bisulfite to remove the liberated iodine. After filtering, washing with water, and drying *in vacuo*, there was obtained 1.85 g. (60%) of product which softened at 134–135° and melted at 137–139°. Recrystallization in the presence of activated carbon (Nuchar) from an ethanol-water mixture afforded deep yellow crystals, m.p. 139–140°. It gave a positive test for the presence of two nitro groups (blue color) with 10% NaOH.

Anal. Calc'd for $C_5H_3IN_2O_4S$: C, 19.11; H, 0.95; N, 8.92.

Found: C, 18.89; H, 0.86; N, 8.99.

2,2',4,4'-Tetranitro-5,5'-dimethyl-3,3'-bithienyl. 4-Iodo-3,5-dinitro-2-methylthiophene (0.94 g., 0.003 mole) was treated with 0.86 g. (0.0135 mole) of Baker's precipitated copper at 148–153°; the addition was carried out in the course of 25 minutes with constant stirring.

After the final addition, the temperature was raised to 155° and 15 minutes. The residual mass then was subjected to the action of boiling benzene in a Soxhlet apparatus for 22 hours. The benzene then was removed from the resulting solution by heating on a steam-bath *in vacuo* to afford a dark-brown solid residue. The latter material was dissolved in ethanol, treated with activated carbon (Norit) and brought to the cloud point with boiling water. There was obtained 0.160 g. (29%) of the desired product which consisted of light tan needles, m.p. 185–186°.

Anal. Calc'd for $C_{10}H_6N_4O_8S_2$: C, 32.09; H, 1.60.
Found: C, 31.75; H, 1.47.

3,5-Dinitro-2-chlorothiophene was prepared by a modification of the existing procedure (11). The modification entailed the nitration of 2-chlorothiophene followed by the direct formation of the desired product without isolation of the mononitro compound. This resulted in an over-all yield of 41%. The material consisted of yellow leaflets, which melted at 120–121°.

4-Nitro-5-chloro-2-acetothienone was synthesized by nitrating 5-chloro-2-acetothienone. Here again, a modification of the existing procedure was applied. This involved first dissolving 5-chloro-2-acetothienone in concentrated sulfuric acid and then adding the required amount of mixed acid with stirring at 0–5°. There was obtained a 78% yield of product, which consisted of light yellow crystals, m.p. 84–86.5°.

Methyl 4-nitro-5-chloro-2-thenoate was synthesized by nitrating methyl 5-chloro-2-thenoate with mixed acid at 0–5° according to the method of Hurd and Kreuz to give a 53% yield of the product which crystallized from methanol in the form of almost colorless needles melting at 84.5–86°.

3,3',5,5'-Tetranitro-2,2'-bithienyl. In the usual apparatus was placed 2.09 g. (0.010 mole) of 3,5-dinitro-2-chlorothiophene. The test tube was heated in a silicone oil-bath to 205° and then the mixture was treated with 2.54 g. (0.04 mole) of copper in the course of 20 minutes with constant stirring; during this time the temperature was maintained at 210–215°. After the final addition, the temperature was raised to 220° for 10 minutes. The cooled reaction mass then was ground to a powder and extracted with acetone in a Soxhlet apparatus for 15 hours. Removal of the solvent *in vacuo* afforded a residual mass, which after two recrystallizations from glacial acetic acid consisted of 0.750 g. (43%) of yellow needles melting at 188–190° with softening at 181°. Upon sublimation *in vacuo* at 200–210°/3 mm., the compound melted at 194.5–196°.

Anal. Calc'd for $C_8H_2N_4O_8S_2$: C, 27.75; H, 0.58; N, 16.18.
Found: C, 28.81; H, 0.73; N, 16.06.

3,3'-Dinitro-5,5'-diacetyl-2,2'-dithienyl. 4-Nitro-5-chloro-2-acetothienone (1.40 g., 0.00681 mole) and copper (1.73 g., 0.02724 mole) were treated in the usual manner at 200–205° in the course of 30 minutes; the final heating was carried out at 215° for 15 minutes. The reaction mixture then was worked up *via* the same procedure employed for the tetranitro compound to afford 0.455 g. (39%) of yellow crystals that melted at 126–127° with softening at 117°. A further recrystallization from aqueous-acetic acid deposited pale lemon yellow crystals melting at 128.5°.

Anal. Calc'd for $C_{12}H_8N_2O_6S_2$: C, 42.35; H, 2.37; N, 8.23.
Found: C, 42.57; H, 3.27; N, 7.92.

3,3'-Dinitro-5,5'-dicarbomethoxy-2,2'-bithienyl. Methyl 4-nitro-5-chloro-2-thenoate (3.40 g., 0.01535 mole) was treated with copper (3.90 g., 0.0614 mole) at 205–210° in the course of 35 minutes with constant stirring. When the addition was complete, the temperature was raised to 225° for 15 minutes. The reaction mixture then was worked up in the usual manner employing acetone as the extracting solvent, and there was obtained a reddish-brown residual material which upon recrystallization from aqueous-acetic acid containing Nuchar gave 1.5 g. (53%) of yellow needles melting at 165–169°. A further recrystallization from the same solvent raised the melting point to 168–169.5°.

Anal. Calc'd for $C_{12}H_8N_2O_8S_2$: C, 38.71; H, 2.17; N, 7.52.
Found: C, 39.05; H, 2.11; N, 7.28.

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Microanalyses were performed by A. A. Sirotenko, formerly of this Department, Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

SUMMARY

Several new β-phenylthiophenes and 2,2′- and 3,3′-bithienyls containing bulky substituents in the *ortho* positions have been prepared from the corresponding halides *via* the Ullmann reaction. It was found that the use of acetone as an extraction solvent substantially increased the yields of the 3,3′-dinitro-2,2′-bithienyls. The preparation of a 3-thienyl halide possessing two *ortho* nitro groups has been achieved by a novel approach. An improved method of synthesis for 2,5-dimethylthiophene has resulted in greatly increased yields.

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